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**HIGH PRODUCTION VOLUME (HPV)
CHEMICAL CHALLENGE PROGRAM**

FINAL SUBMISSION

for

ROSIN ESTERS

**CAS No. 8050-26-8
CAS No. 8050-31-5
CAS No. 68153-38-8
CAS No. 68186-14-1
CAS No. 65997-13-9
CAS No. 64365-17-9
CAS No. 8050-15-5**

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By

**The Pine Chemicals Association, Inc.
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HPV Task Force**

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Final Submission for Rosin Esters

Summary

As part of the High Production Volume (HPV) Program, the Pine Chemicals Association, Inc. (PCA) has sponsored 19 substances of the rosin family. Final Submissions for rosin and rosin salts (comprising six substances) and rosin adducts (comprising six substances) have been prepared and submitted. This final submission addresses the following six chemicals, known collectively as Rosin Esters:

CAS No. 8050-26-8, Rosin, pentaerythritol ester
CAS No. 8050-31-5, Rosin, glycerol ester
CAS No. 68153-38-8, Rosin, diethylene glycol ester
CAS No. 68186-14-1, Rosin, methyl ester
CAS No. 65997-13-9, Rosin, hydrogenated, glycerol ester
CAS No. 64365-17-9, Rosin, hydrogenated, pentaerythritol ester
CAS No. 8050-15-5, Rosin, partially hydrogenated, methyl ester

All of the members of this group of substances are closely related to rosin, a naturally occurring substance found in trees, predominantly pine trees. Rosin is composed primarily of resin acids, a class of tricyclic carboxylic acids, but also contains minor amounts of dimerized rosin, fatty acids and unsaponifiable matter. All the members of this group are esters of rosin that are made by reacting rosin with selected alcohols or polyols at elevated temperatures. As with other rosin-based products, these substances are complex mixtures and, therefore, are Class 2 substances.

The physical properties of rosin esters depend to a large extent on the hydroxy compound used to prepare the ester and can range from liquids to brittle solids. The largest end use for these rosin esters is as tackifiers in a wide variety of adhesive formulations. The specific rosin ester selected depends on the properties required in the final adhesive.

There were substantial amounts of data on rosin, pentaerythritol ester; rosin, glycerol ester; rosin, hydrogenated, glycerol ester; and rosin, hydrogenated, pentaerythritol ester for many SIDS endpoints. These data demonstrate that these compounds are non-toxic in acute toxicity tests in multiple species. Existing data from repeat-dose studies, including long-term carcinogenicity studies, show low toxicity and no potential carcinogenic or reproductive effects.

Where applicable, PCA conducted physical/chemical property and environmental fate testing on all of the substances in this category for which data were not already available. PCA elected to treat this group of chemicals as a category for purposes of the HPV program. Rosin, pentaerythritol ester (CAS# 8050-26-8) and rosin, partially hydrogenated, methyl ester (CAS# 8050-15-5) were selected

as the representative substances in this category for testing for the additional SIDS data. These two substances represent the extremes of the properties of the members of this category -- with the pentaerythritol ester having the highest molecular weight and the methyl ester, the lowest. Further, both of these substances are commercially important.

The two representatives of the category were also used for ecotoxicity and developmental toxicity testing. Most of the other required mammalian toxicity data (with the exception of acute oral toxicity) were available for one of the representatives of this category (rosin, pentaerythritol ester). Additional mammalian toxicity testing was only conducted on the other representative compound (rosin, partially hydrogenated, methyl ester).

The totality of the SIDS data for the substances in this category is briefly summarized below and in Tables 1-3. As shown in these summaries, because rosin, pentaerythritol ester and rosin, partially hydrogenated, methyl ester are non-toxic in both mammalian and aquatic test systems, it is reasonable to conclude that all substances in this category are similarly non-toxic. These data are described and discussed in the main document. Detailed Robust Summaries of all relevant data are appended to this document.

Physical/Chemical Properties

Physical and chemical properties were determined where appropriate; however, many of these endpoints are either inappropriate or cannot be measured for these compounds:

- Melting or boiling points were not determined because these substances will either will not give a sharp melting point when heated or will decompose before they melt or boil.
- Under ambient conditions, the vapor pressure of these substances is essentially zero and experimental measurement is not possible.
- Water solubility and partition coefficients are summarized in Table 1. It should be noted that considerable effort was undertaken to accurately determine water solubility.
- With respect to the partition coefficient (K_{ow}), the approved method (OECD 117) yields a range of values rather than a single value representative of the mixture as summarized in Table 1. The range of values reflects the partition coefficients of the individual constituents of these complex mixtures.

—The details on these test results are provided in the Robust Summaries.

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Table 1. Summary of Physical/Chemical and Environmental Fate Data*

Chemical	Required SIDS Endpoints		
	Partition Coefficient	Water Solubility (mg/l)	Percent Biodegradation At 28 Days
Rosin, pentaerythritol ester	6.1 – 7.1	0.38	0.0
Rosin, glycerol ester	No values >1.5	1.5	0.0
Rosin, diethylene glycol ester	4.0 – 5.8	<0.40	19.7
Rosin, methyl ester	4.9 – 7.6	5.2	50.7
Rosin, hydrogenated, glycerol ester	4.7 – 5.8	0.15	47.3
Rosin, hydrogenated, pentaerythritol ester	4.6 – 7.3	<0.22	3.0
Rosin, partially hydrogenated, methyl ester	6.4 – 7.6	2.10	28.3

*No testing was conducted for melting point, boiling point, vapor pressure, hydrolysis, photodegradation, and transport and distribution between environmental compartments as explained in main document.

Environmental Fate

The SIDS environmental fate endpoints were determined where appropriate; however, many of these endpoints are either inapplicable or cannot be measured for these compounds.

- Photodegradation was not relevant, since the vapor pressure of these compounds is essentially zero and they could not enter the atmosphere.
- Hydrolysis in water was not determined for any of the compounds in this category because all have low water solubility and also lack a functional group that would be susceptible to hydrolysis.
- Transport and distribution between environmental compartments (i.e., fugacity) was not determined due to the inability to provide usable inputs to the required model.
- Biodegradation data are summarized in Table 1 and show that none of these substances are substantially biodegradable in the environment.

The details on these test results are provided in the Robust Summaries.

Ecotoxicity

Rosin, pentaerythritol ester and rosin, partially hydrogenated, methyl ester were tested for acute toxicity to fish, daphnia and algae at the maximum measured water solubility. These data are summarized in Table 2 and show that with the exception of an inexplicable result in daphnia for rosin, partially hydrogenated, methyl ester, none of the compounds in this category are toxic to algae, daphnia or fish. The details of these test results are provided in the Robust Summaries.

Table 2. Summary of Ecotoxicity Data

Chemical Name	Required SIDS Endpoint		
	Acute Fish 96 hr NOEL _r	Acute Daphnia 48 hr NOEL _r	Acute Algae 72 hr NOEL _r
Rosin, pentaerythritol ester	1000 mg/l	1000 mg/l	1000 mg/l
Rosin, glycerol ester	C	C	C
Rosin, diethylene glycol ester	C	C	C
Rosin, methyl ester	C	C	C
Rosin, hydrogenated, glycerol ester	C	C	C
Rosin, hydrogenated, pentaerythritol ester	C	C	C
Rosin, partially hydrogenated, methyl ester	1000 mg/l	19 mg/l	1000 mg/l

C = Indicates category read-down from available data

NOEL_r = no observed effect loading rate

Mammalian Toxicity

Data were generated for rosin, pentaerythritol ester on acute toxicity and reproductive and developmental effects and for rosin, partially hydrogenated methyl ester on acute and repeat dose toxicity, genotoxicity and reproductive and developmental effects. These mammalian toxicity data are summarized in Table 3 and demonstrate that rosin, pentaerythritol and rosin, partially hydrogenated methyl ester are non-toxic. The inability to establish a NOEL for rosin, partially hydrogenated methyl ester was likely due to “severe” palatability issues at all dose levels. Based on the category approach, results for these two test substance also represent other members of the category. The details of these test results are provided in the Robust Summaries.

Table 3. Summary of Mammalian Toxicity Data

Chemical Name	Required SIDS Endpoints					
	Acute Oral	Repeat Dose	In vitro genetox (Mutation)		In vitro genetox (Chrom. Ab.) ^a	
Rosin, pentaerythritol ester	LD ₅₀ > 2000 mg/kg	NOEL > 1500 mg/kg/day	No tumors in 2 yr. cancer bioassay ^a		No tumors in 2 yr. cancer bioassay ^a	
Rosin, glycerol ester	C	NOEL = 1000 mg/kg/day	+S9 Neg.	-S9 Neg.	+S9 Neg.	-S9 Neg.
Rosin, diethylene glycol ester	C	C	C	C	C	C
Rosin, methyl ester	LD ₅₀ > 5000 mg/kg	C	C	C	C	C
Rosin, hydrogenated, glycerol ester	C	NOEL = 1000 mg/kg/day	C	C	C	C
Rosin, hydrogenated, pentaerythritol ester	C	C	C	C	C	C
Rosin, partially hydrogenated, methyl ester	LD ₅₀ > 2000 mg/kg	NOEL < 400 mg/kg/day ^a	+S9 Neg.	-S9 Neg.	+S9 Neg.	-S9 Neg.

C = Indicates category read-down or read-up from available data.

a = see main document for additional explanation.

Overall Hazard Evaluation and Potential Exposure

For potential human health effects, the totality of the SIDS data demonstrate that rosin, pentaerythritol ester and rosin, partially hydrogenated, methyl ester are non-toxic. Additional toxicity data for rosin, glycerol ester and rosin hydrogenated, glycerol confirms the lack of toxicity of the substances in this category. Accordingly, based on the category approach, it can be inferred that all of the substances in this group are also non-toxic.

Both rosin pentaerythritol ester and rosin, partially hydrogenated, methyl ester have no acute oral toxicity (i.e., LD₅₀'s > 2,000 mg/kg). Repeat dose toxicity data for rosin pentaerythritol ester demonstrates a no observed effect level (NOEL) of >1500 mg/kg/day and a NOEL of >1500 mg/kg/day for reproductive and developmental effects. The NOEL for repeat dose toxicity and reproductive/developmental effects for rosin, partially hydrogenated, methyl ester was less than the lowest dose tested (i.e., 400 mg/kg/day). However, the effects observed were a consequence of "severe" palatability issues at all dose levels. The lack of repeat dose toxicity (i.e., NOEL's of 1000 mg/kg/day) for rosin, glycerol ester and rosin hydrogenated, glycerol ester is confirmatory of the lack of toxicity of the substances in this category. The lack of carcinogenic effects in a two-year feeding study for rosin, pentaerythritol ester suggests that this substance would not be mutagenic. The lack of *in vitro* genotoxicity (i.e., mutations and chromosomal aberrations) for rosin, glycerol ester and rosin hydrogenated, glycerol ester is confirmatory of the lack of genotoxicity of the substances in this category.

Consequently, no adverse health consequences would be associated with exposures to any of the rosins esters in this category. For potential ecotoxicological effects, the data on rosin, pentaerythritol ester and rosin, partially hydrogenated methyl ester demonstrate that all of the substances in this category are non-toxic to aquatic organisms.

With respect to potential exposure to the substances in this category, all are consumed almost entirely in the production of other chemical intermediates. Rosin is reacted in a variety of ways to form salts, adducts, esters, dimers and other reaction products which find application in the production of printing inks, adhesives (primarily hot melt packaging adhesives), paper size, and coatings. These uses would be considered non-dispersive in that the rosin derived chemical is reacted or otherwise contained within the article in which it is being used. It is estimated that greater than 80% of the various rosin derivatives are used in the type of applications described above. As such inhalation exposure or volatilization to air is minimal due to a lack of vapor pressure for these substances. Exposure in the listed applications is generally limited to dermal contact during the processing, finishing and shipping of the products of which they become a part. Approximately 3% of rosin is reacted to form specific rosin esters which are marketed to the chewing gum industry. These derivatives are approved for direct food contact by the US FDA

The Pine Chemicals Association, Inc. HPV Task Force includes the following companies:

Akzo Nobel Resins
Akzo Nobel - Eka Chemicals Incorporated
Arizona Chemical Company
Asphalt Emulsion Manufacturers Association
Boise Cascade Corporation
Cognis Corporation
Crompton Corporation
Eastman Chemical Co. (including the former Hercules Inc. Resins Division)
Georgia-Pacific Resins Inc.
Hercules Incorporated
ICI Americas (including the former Uniqema)
Inland Paperboard & Packaging, Inc.
International Paper Co. (including the former Champion International Corporation)
Koch Materials Co.
McConaughay Technologies, Inc.
Mead Corp.
Packaging Corporation of America
Plasmine Technology, Inc.
Raisio Chemicals
Rayonier
Riverwood International
Smurfit – Stone Container Corporation
Westvaco
Weyerhaeuser Co.

The PCA HPV Task Force has filed multiple test plans covering various chemicals. Not all members of the Task Force produce the substances covered by this final submission.

I. Description of Rosin Esters

The Pine Chemicals Association, Inc. (PCA) has sponsored seven HPV chemicals known collectively as Rosin Esters. The Test Plan for this group of substances was posted on EPA's HPV website on February 26, 2002, with comments from the EPA, the Physicians Committee for Responsible Medicine (PCRM) and Environmental Defense posted on December 10, 2002, October 14, 2002, and August 20, 2002, respectively. After reviewing these comments, PCA prepared a response which was subsequently posted on EPA's HPV website on October 22, 2003.

This group of substances consists of the following:

CAS No. 8050-26-8, Rosin, pentaerythritol ester
CAS No. 8050-31-5, Rosin, glycerol ester
CAS No. 68153-38-8, Rosin, diethylene glycol ester
CAS No. 68186-14-1, Rosin, methyl ester
CAS No. 65997-13-9, Rosin, hydrogenated, glycerol ester
CAS No. 64365-17-9, Rosin, hydrogenated, pentaerythritol ester
CAS No. 8050-15-5, Rosin, partially hydrogenated, methyl ester

Rosin is a naturally occurring substance found in trees, predominantly pine trees. Rosin is composed primarily of rosin acids, a class of tricyclic carboxylic acids, but also contains minor amounts of dimerized rosin, fatty acids and unsaponifiable matter. Six rosins and rosin salts are addressed in another Final Submission.

All the members of this category of substances are esters of rosin, made by reacting rosin with selected alcohols or polyols. The esterification reactions between rosin and various hydroxy compounds are shown schematically in Figures 1-4 below. These figures illustrate that the carboxylic acid group of the rosin reacts with the hydroxyl group of the alcohol or polyol, with the elimination of water.

In order for esterification to take place, the chemical reactions for producing the various rosin esters are carried out at elevated temperatures to remove the water of reaction. With esterification reactions involving polyols, temperatures in excess of 250 °C are generally required in order to force the reaction towards completion. Because the rosin molecule is very large compared to the small polyol molecules and because the acid group of rosin is tertiary, a great amount of energy is required to overcome the steric effects. In actual practice, complete esterification is never achieved and all rosin esters contain small amounts (ca 5%) of unreacted rosin (Zinkel and Russell 1989). As with other rosin-based

products, these substances are complex mixtures and, therefore, are Class 2 substances.¹

A. Composition

The physical properties of rosin esters depend to a large extent on the hydroxy compound used to prepare the ester and can range from liquids to brittle solids. The largest end use for these rosin esters is as tackifiers in a wide variety of adhesive formulations. Various rosin esters are used in solvent-based, water-based and hot-melt adhesives, with the specific ester selected dependent on the properties required in the final adhesive.

As previously noted, rosin esters are synthesized from rosin that is derived primarily from pine trees. The composition of rosin is described in the PCA's *Final Submission for Rosin and its Salts*, and the reader is referred to that document for detailed information. The general characteristics and composition of the rosin esters in this category are addressed below.

1. Rosin, pentaerythritol ester (CAS# 8050-26-8) and Rosin, hydrogenated, pentaerythritol ester (CAS# 64365-17-9)

These substances are made by reacting rosin or hydrogenated rosin with pentaerythritol at a temperature of about 270⁰C. The reaction is shown schematically in Figure 1. Pentaerythritol, with four hydroxyl groups, is capable of forming a tetraester. Because of steric effects, the reaction is not completely achieved even at the high temperatures used. Therefore, the commercial products are primarily a combination of tetraesters and triesters, with some di and mono ester, as well as a small amount of unreacted rosin. The only difference between the esters of rosin and hydrogenated rosin is that, in hydrogenated rosin ester, the double bonds in the rosin are removed prior to esterification with the aim of giving the final ester greater oxidative stability. The substances are brittle glass-like solids ranging in color from very pale yellow to pale brown. They do not have a true melting point, but they have a softening point of about 100⁰C.

¹ As defined in the TSCA Inventory, "In terms of composition, some chemical substances are single compounds composed of molecules with particular atoms arranged in a definite known structure. For purposes of this discussion, such substances will be denoted Class 1 substances. Many commercial chemical substances are not in this class. They may have variable compositions or be composed of a complex combination of different molecules. These substances will be denoted Class 2 substances."

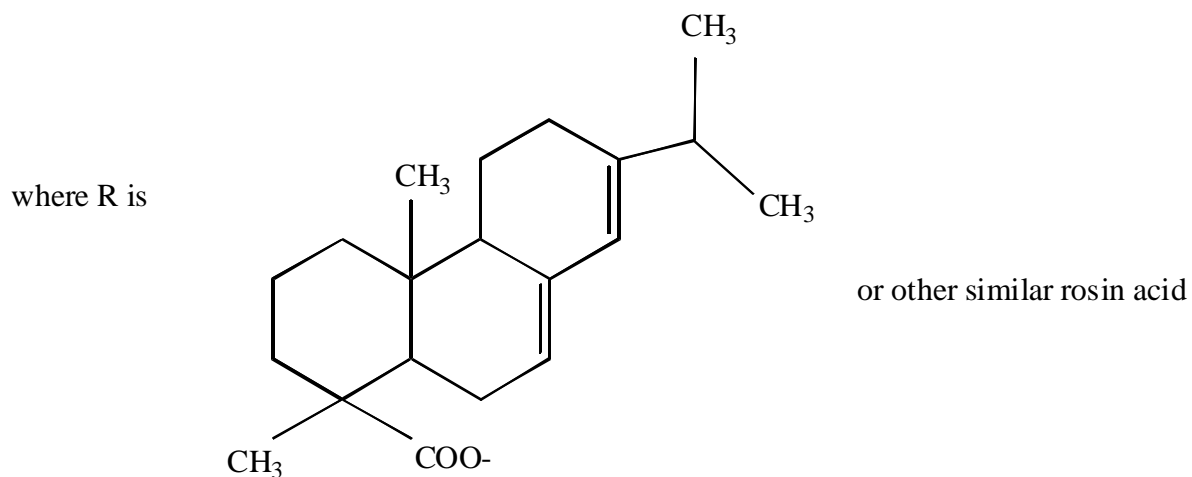
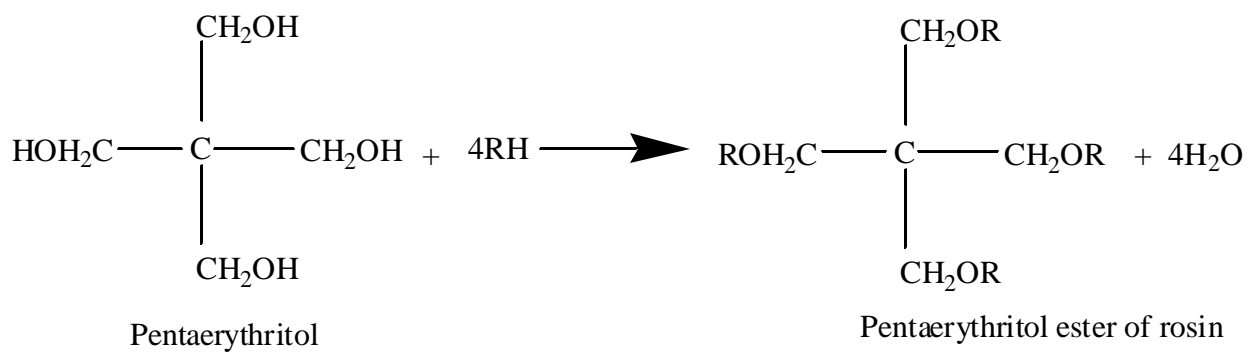
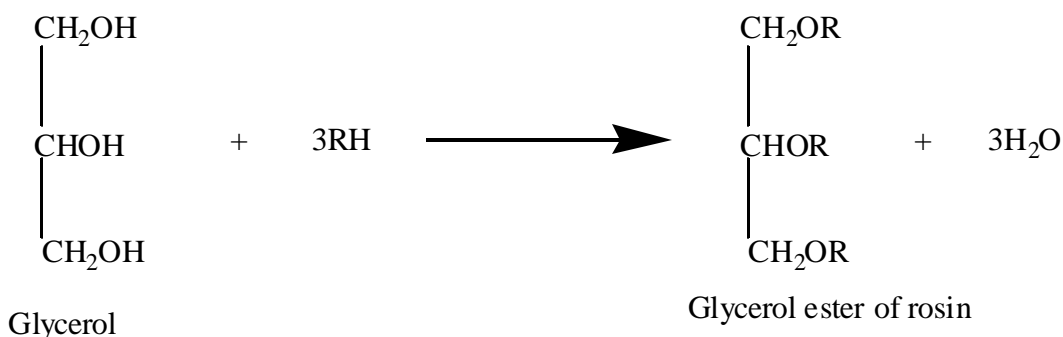


Figure 1. Formation of the pentaerythritol ester of rosin

2. Rosin, glycerol ester (CAS # 8050-31-5) and Rosin, hydrogenated, glycerol ester (CAS# 65997-13-9)

These substances are made by reacting rosin or hydrogenated rosin with glycerol at a temperature of about 250°C. The reaction is shown schematically in Figure 2. Glycerol, with three hydroxyl groups, is capable of forming a triester. Because of the steric effects of the reaction, the reaction cannot be completely achieved even at the high temperatures used, and the commercial products are primarily a combination of triesters and diesters, with small amounts of monoesters and unreacted rosin. Again, the only difference between the glycerol esters of rosin and hydrogenated rosin is that, in the latter, the double bonds in the rosin are removed prior to esterification with the aim of giving the final ester greater oxidative stability. Like the pentaerythritol esters, these esters are also brittle glass-like solids ranging in color from very pale yellow to pale brown. They do not have a true melting point, but they have a softening point of about 85°C.

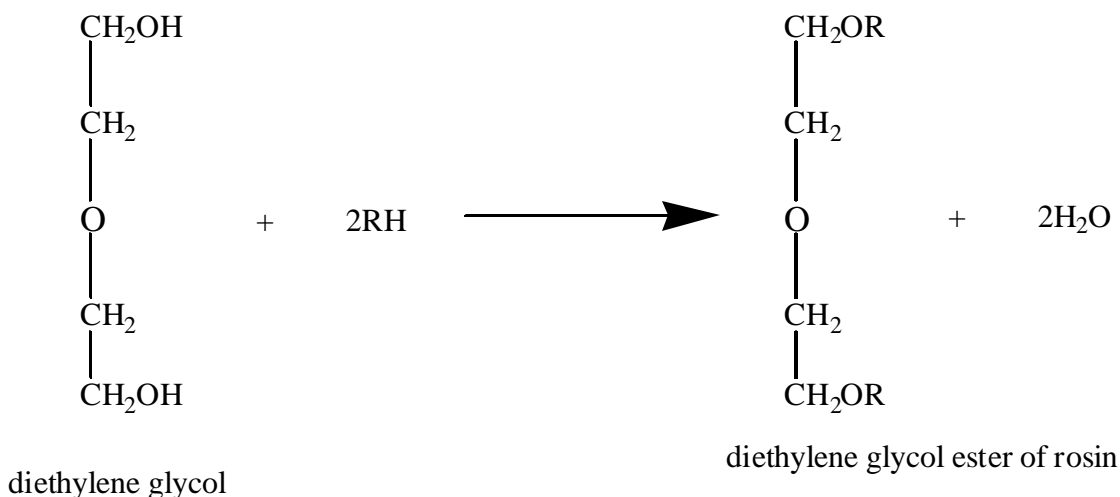


where R is as defined in Figure 1

Figure 2. Formation of the glycerol ester of rosin

3. Rosin, diethylene glycol ester (CAS # 68153-38-8)

This substance is made by reacting rosin or hydrogenated rosin with diethylene glycol at a temperature of about 250°C. The reaction is shown schematically in Figure 3. Diethylene glycol, with two hydroxyl groups, is capable of forming a diester. As a consequence of steric effects, the commercial products contain both di and mono esters, as well as a small amount of unreacted rosin. The substance is a viscous liquid at room temperature and is pale yellow in color.

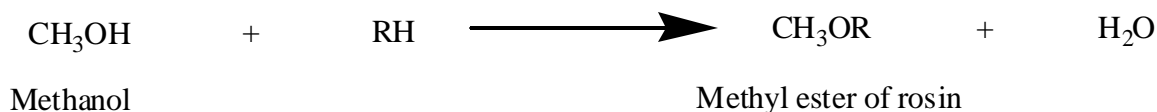


where R is as defined in Figure 1.

Figure 3. Formation of the diethylene glycol ester of rosin

4. Rosin, methyl ester (CAS#68186-14-1) and Rosin, partially hydrogenated, methyl ester (CAS# 8050-15-5)

These substances are made by reacting rosin or hydrogenated rosin with methanol at an elevated temperature. These reactions are carried out at a lower temperature than the glycerol or pentaerythritol esterifications because of the low boiling point of methanol. In this case, the reversible reaction is forced toward the ester by using excess alcohol as well as elevated temperature. The reaction is shown schematically in Figure 4. Because methanol is monohydric, only one ester is formed. Again, the only difference between the methyl esters of rosin and hydrogenated rosin is that, in the latter, the double bonds in the rosin are removed prior to esterification with the aim of giving the final ester greater oxidative stability. The methyl esters are free-flowing liquids with colors ranging from almost water white to pale yellow.



where R is as defined in Figure 1.

Figure 4. Formation of the methyl ester of rosin.

B. Commercial Uses of Rosin Esters

Esters of rosin are found in several different end use markets, especially hot melt and pressure sensitive adhesives, and chewing gum. Hot melt adhesives are a major use area for rosin esters. Applications include all types of packaging, book-binding, and disposable diaper construction. Tackifiers used for hot melt adhesives are primarily pentaerythritol esters. These are preferred over glycerol esters in hot melt applications primarily due to oxidative resistance combined with higher softening points. Aqueous dispersions of rosin esters are used in the rapidly growing pressure sensitive adhesives market. Simple glycerol esters of rosin are used in chewing gum as a tackifier. These substances are approved for use by FDA as direct food additives in chewing gum under 21 CFR § 172.615 (a).

C. Complexity of Analytical Methodology

All the substances in this category are Class 2 substances. This, combined with fact that they are essentially insoluble in water and, with two exceptions, decompose rather than vaporize on heating creates a variety of analytical challenges. Gas chromatography is applicable to the analysis of the two methyl esters but not the other esters. The most feasible approach for the analysis of the non-methyl esters was determined to be size exclusion gel permeation chromatography. Although this technique separates components based on size rather than chemical composition, studies determined that it was generally applicable to the non methyl esters. Because the solubility of rosin esters is so low (<10 ppm) the reliability of this analytical method was verified at such low concentrations.

II. Rationale for Selection of Representative Compounds for Testing

Rosin, pentaerythritol ester (CAS # 8050-26-8) and rosin, partially hydrogenated, methyl ester (CAS # 8050-15-5) were selected as the representative substances in this category for testing for the applicable SIDS endpoints. These two substances represent the extremes of the properties of the members of this group. Pentaerythritol ester has the highest molecular weight and the methyl ester, the lowest. This molecular weight range manifests itself with the pentaerythritol ester having the highest softening point and the methyl ester the lowest. Consequently, the selection of these two substances as representatives of this category is consistent with the EPA guidelines since their molecular weights bracket the category. Further, both of these substances are commercially important, with the pentaerythritol ester being one of the highest volume rosin derivatives produced in the United States.

Another criterion listed by EPA for grouping chemicals into a category is the use of the "family approach" of examining related chemicals. Since all of the chemicals in this category are esters of rosin, they are in the same family of compounds. In summary, this group of chemicals fits the requirements of the EPA's HPV Challenge program for a chemical category, and rosin, pentaerythritol ester and rosin, partially hydrogenated, methyl ester are the most appropriate representative test materials from this category.

In their comments on the *Test Plan for Rosin Esters*, EPA, while agreeing that the grouping was generally well supported, questioned the justification of rosin, partially hydrogenated methyl ester as one of the representative compounds for this category. The Agency recommended that rosin methyl ester (instead of rosin partially hydrogenated methyl ester) should be used as the second representative test substance. EPA believed that rosin methyl ester, as an unsaturated ester, may undergo epoxidation during metabolism and therefore be more toxicologically active. Although this is a hypothetical possibility (because some compounds can undergo epoxidation in biological systems) there is no evidence in the literature that rosin methyl ester would be susceptible to epoxidation in a biological system. Furthermore, since the LD50's of both the rosin methyl ester and rosin partially hydrogenated methyl ester are >2000 mg/kg, there is no basis for assuming that the rosin methyl ester would be more toxic. In addition, the lack of repeat dose toxicity (i.e., NOEL's of 1000 mg/kg/day) and *in vitro* genotoxicity for rosin, glycerol ester and rosin hydrogenated glycerol ester is confirmatory of the lack of toxicity of the substances in this category. Further, it also should be noted that the relative production and commercial importance of rosin, partially hydrogenated methyl ester is far greater than that of the rosin methyl ester. Accordingly, rosin, partially hydrogenated methyl ester was used as the second representative test substance in this category.

III. Summary of Data

Where applicable, physical/chemical property and environmental fate testing was conducted on all of the substances in the group. With respect to toxicological testing, rosin pentaerythritol ester and rosin partially hydrogenated methyl ester were selected as representatives of the category and used for the required ecotoxicity and mammalian toxicity testing. Table 4 summarizes the results from all of the testing conducted on the substances in this category.

A. Physicochemical Data

The basic physicochemical data required in the SIDS battery includes melting point, boiling point, vapor pressure, partition coefficient (K_{ow}), and water solubility.

Some of these measures are inapplicable given the nature of the materials. Moreover, Class 2 substances are composed of a complex mixture of substances and are often difficult to characterize. Rosin esters are not only Class 2 substances, but also are derived from natural sources. Therefore, their composition is variable and cannot be represented by a single chemical structural diagram. Due to this “complex mixture” characteristic of rosin esters, some physical property measurements, such as partition coefficient, do not give single definitive results because the methodology used to determine these properties will actually fractionate or partition the substance into various components. Consequently, some results are likely to be erroneous, difficult to interpret, or meaningless.

1. Melting Point

Due to their complex nature, none of the members of this category have a well-defined melting point. The four rosin esters that are solids at ambient temperatures soften when heated and so have softening points rather than a true melting point. As noted above, the softening point of the two glycerol esters is about 85 °C while the softening point for the two pentaerythritol esters is about 100 °C. Consequently, the melting point of these substances was not measured.

2. Boiling Point

With the exception of the methyl esters, all of the members of this category are produced by high temperature reactions and are non-volatile solids at ambient temperatures. A boiling point under ambient conditions has no significance because these materials will thermally decompose before they boil. While liquids, the methyl esters would also decompose before they boil. Accordingly, measurement of this property was inappropriate for all the substances in this category.

Table 4
Summary of Data
Rosin Esters*

Chemical and CAS #	Required SIDS Endpoints										
	Partition Coef.	Water Sol. Mg/l	Biodeg. % @ 28 Days	Acute Fish NOELr	Acute Daph. NOELr	Acute Algae NOELr	Acute Oral LD ₅₀	Repeat Dose NOEL	Genetox Mutation (<i>Salmonella</i>)	Genetox Chrom. Ab.	Repro Develop. NOEL
Rosin, pentaerythritol ester 8050-26-8	6.1 – 7.1	0.38	0.0	1000 mg/l	1000 mg/l	1000 mg/l	>2000 mg/kg	1000 mg/kg/d	No tumors in 2 yr feeding study	No tumors in 2 yr feeding study	> 1500 mg/kg/d
Rosin, glycerol ester 8050-31-5	No values > 1.5	<0.4	0.0	C	C	C	C	1000 mg/kg/d	Neg. ± S9	Neg. ± S9	1000 mg/kg/d (repro)
Rosin, diethylene glycol ester 68153-38-8	4.0 – 5.8	2.38	19.7	C	C	C	C	C	C	C	C
Rosin, methyl ester 68186-14-1	4.9 – 7.6	5.2	50.7	C	C	C	>5000 mg/kg	C	C	C	C
Rosin, hydrogenated glycerol ester 65997-13-9,	4.7 – 5.8	0.15	47.3	C	C	C	C	C	C	C	C
Rosin, hydrogenated pentaerythritol ester 64365-17-9,	4.6 – 7.3	<.22	3.0	C	C	C	C	C	C	C	C
Rosin, partially hydrogenated methyl ester 8050-15-5	6.4 – 7.6	2.10	28.3	1000 mg/l	19 mg/l	1000 mg/l	>2000 mg/kg	< 400 mg/kg/d	Neg. ± S9	Neg. ± S9	< 400 mg/kg/d

C - Indicates category read-down or read-up from data on various rosin esters.

* No testing was conducted for melting point, boiling point, vapor pressure, hydrolysis, photodegradation and transport and distribution between environmental compartments as explained in the text.

In commenting on the Test Plan for Rosin Esters with respect to the boiling point, EPA noted that according to OECD Guideline 103 “*measurements at reduced pressure may be appropriate for substances with a high boiling point and substances which decompose at elevated temperatures.*” However, the relevance of conducting this kind of testing for any HPV substance -- much less for any of the substances in this category -- is highly questionable when the test data are to be reported at ambient conditions. All of the substances in this category will decompose well before they boil at ambient pressure. Data on boiling points at elevated temperatures and reduced pressure (i.e., below ambient) would only be relevant for designing fractional distillation processes. Consequently, as noted above, no determination of boiling points for any of the substances in this category was undertaken.

3. Vapor Pressure

Vapor pressures for the rosin esters (four of which are solids at ambient temperatures, two of which are viscous liquids and one which is a liquid) are effectively zero, and their experimental measurement is inappropriate. In commenting on the *Test Plan for Rosin Esters*, EPA suggested that the vapor pressure of randomly selected individual components of the complex mixture of chemicals that comprise any of the rosin esters (i.e., various diesters, trimesters and small amounts of unreacted rosin acids) would be representative of the entire mixture. However, there is further complexity with respect to these substances due to the presence of numerous resin acids, including abietic, dehydroabietic, neoabietic, pimaric, sandarcopimaric, communic, palustric, and isopimaric, all of which are esterified. Therefore, there is no basis for assuming that an estimated vapor pressure of any component of the mixture would be representative of the entire mixture. Consequently, measurement of this property for the rosin esters is inappropriate.

4. Water Solubility

The water solubility of the six compounds in this category was determined using OECD (105).

Table 5

Chemical	Water Solubility (mg/l)
Rosin, pentaerythritol ester	0.38
Rosin, glycerol ester	<0.4
Rosin, diethylene glycol ester	2.38
Rosin, methyl ester	5.20
Rosin, hydrogenated, glycerol ester	0.15
Rosin, hydrogenated, pentaerythritol ester	<0.22
Rosin, partially hydrogenated, methyl ester	2.10

All of these data are presented in detail in the Robust Summaries.

5. Partition Coefficient

The partition coefficients (i.e., K_{ow}) for all of the compounds in this category were determined. Because all of these substances are Class 2 mixtures, the procedure (OECD 117) to determine the K_{ow} typically yields a range of K_{ow} values rather than a single value representative of the mixture. Thus, the results reflect the partition coefficients of the components rather than the mixture. The partition coefficient data are shown below in Table 6.

Table 6

Chemical	Partition Coefficient (K_{ow})
Rosin, pentaerythritol ester	6.1 – 7.1
Rosin, glycerol ester	No values > 1.5
Rosin, diethylene glycol; ester	4.0 – 5.8
Rosin, methyl ester	4.9 – 7.6
Rosin, hydrogenated, glycerol ester	4.7 – 5.8
Rosin, hydrogenated pentaerythritol ester	4.6 – 7.3
Rosin, partially hydrogenated methyl ester	6.4 – 7.6

All of these data are presented in detail in the Robust Summaries.

B. Environmental Fate Data

The fate or behavior of a chemical in the environment is determined by the reaction rates for the most important transformation (degradation) processes. The basic environmental fate data covered by the HPV Program include biodegradation, stability in water (hydrolysis as a function of pH), photodegradation and transport and distribution between environmental compartments.

1. Biodegradation

Biodegradability provides a measure for the potential of compounds to be degraded by microorganisms. Depending on the nature of the test material, several standard test methods are available to assess potential biodegradability. One of the chemicals in this category (rosin, partially hydrogenated, methyl ester) had existing data on the biodegradation endpoint. Biodegradation for the other six substances in this category was determined using OECD method 301B. The biodegradation data are shown in Table 7 and demonstrate that none of the substances in this category are substantially biodegradable.

Table 7

Chemical	Percent Biodegradation At 28 Days
Rosin, pentaerythritol ester	0.0
Rosin, glycerol ester	0.0
Rosin, diethylene glycol ester	19.7
Rosin, methyl ester	50.7
Rosin, hydrogenated glycerol ester	47.3
Rosin, hydrogenated pentaerythritol ester	3.0
Rosin, partially hydrogenated methyl ester	28.3

All of these data are presented in greater detail in the Robust Summaries.

2. Hydrolysis

Hydrolysis as a function of pH is used to assess the stability of a substance in water. Hydrolysis is a reaction in which a water molecule (or hydroxide ion) substitutes for another atom or group of atoms present in an organic molecule. Experience has shown that rosin ester molecules are very resistant to hydrolysis. The rosin esters will hydrolyze only under extreme laboratory conditions (i.e., strong alkali and elevated temperatures) which are not normally found in the environment nor are such conditions part of the OECD test protocol. In addition, low water solubility often limits the ability to determine hydrolysis as a function of pH. All of the rosin esters have very low solubility in water. Therefore, these materials are stable in water and it was unnecessary to attempt to measure the products of hydrolysis.

3. Photodegradation

Due to their lack of any vapor pressure under ambient conditions, there is essentially no opportunity for any of these chemicals to enter the atmosphere. Thus, photodegradation is irrelevant. In addition, based on the constituents in these complex mixtures, there is no reason to suspect that they would be subject to breakdown by a photodegradative mechanism. In commenting on the *Test Plan for Rosin Esters*, EPA also suggested that estimated photodegradation based on the vapor pressure of randomly selected individual components of the complex mixture of chemicals that comprise any of the rosin esters could be used for the entire mixture. However, there is no basis for assuming that the vapor pressure of one substance in a multi-substance mixture would be representative of the entire mixture. Consequently, this endpoint was not determined for any of the substances in this category.

4. Transport and Distribution between Environmental Compartments

The transport and distribution between environmental compartments (fugacity) is intended to estimate the ability of a chemical to move or partition in the environment. The determination of this property requires the use of various models. One of the most frequently referenced models is the level III model from the Canadian Environment Modeling Centre at Trent University. Even the simplest of these models requires estimates of solubility, vapor pressure and octanol/water partition coefficient to estimate fugacity for a single component. For complex class 2 substances such as rosin esters, estimates of any one of these physical parameters for the various known components could span a range of more than an order of magnitude. When combining three or more parameters of equally variable ranges to derive estimates for different environmental media, the variability in the estimate for any given medium could grow geometrically to three or more orders of magnitude. This suggests that any estimates based on arbitrarily selected individual components would be essentially useless for any practical purpose. Add to this the additional fact that there is variability in the chemical composition of these substances and the possible permutations become unmanageable. Consequently, for complex mixtures such as rosin esters, the mathematical models which rely upon estimates for individual components are of no practical use in predicting environmental fate. Therefore, due to the inability to provide usable inputs to the required model, no determination of transportation and distribution between environmental compartments was undertaken for rosin ester.

C. Ecotoxicity Data

The basic ecotoxicity data that are part of the HPV Program include acute toxicity to fish, daphnia and algae. While there are some existing data on these endpoints for substances in this category, these data are conflicting and it is impossible to determine which, if any, of these findings is representative of true ecotoxicity. The inconsistencies in how water samples were prepared for testing these endpoints render these data inadequate. Consequently, rosin, pentaerythritol ester and rosin, partially hydrogenated, methyl ester were tested for acute toxicity to fish, daphnia and algae under conditions that maximize the solubility under the specific test exposure conditions, but reduce exposure to insoluble fractions, which may cause nonspecific toxicological effects. In addition, the effect of both filtering, to further minimize nonspecific physical effects, and of reducing the pH to the lower end of the acceptable range for test organism survival, was also investigated for changes in toxicological effects.

In commenting on the *Test Plan for Rosin Esters* EPA disagreed with the decision to conduct acute testing on fish, daphnia and algae for the two representative substances (i.e., rosin PE ester and rosin, partially hydrogenated methyl ester) based on the unsubstantiated assertion that “*chronic toxicity is likely to occur with*

these substances.” Instead, EPA suggested that only a 21-day daphnia test be conducted on a different compound (i.e., rosin, methyl ester) based on the logic that low water solubility and estimated $\log K_{ow} < 7.5$ would somehow translate into greater toxicity. However, as noted in Table 4, none of these complex substances have partition coefficients that can be represented by a single value. For example, the range of $\log K_{ow}$ values for rosin, PE ester and rosin partially hydrogenated methyl ester are 4.6-7.3 and 6.4-7.6, respectively. In comparison, the range of $\log K_{ow}$ values for rosin, methyl ester is 4.9-7.6, representing essentially no difference in the $\log K_{ow}$ values for the two representative substances and the substance suggested by EPA.

An additional basis for EPA's suggestion to test the methyl ester rather than the partially hydrogenated methyl ester was that *“Because the calculated log Kow for CAS No. 68186-14-1 is lower than that for CAS No. 8050-15-5 it is the preferred test substance.”* However, as illustrated above in Table 4, these mixtures exhibit a range of K_{ow} values rather than a single value so none of these substances has a $\log K_{ow}$ value that can be described by a single number. Finally, there does not appear to be any basis for EPA's claim that only rosin, methyl ester would exhibit aquatic toxicity and that *“other category members will not show aquatic acute or chronic effects based on their physiochemical properties.”* Consequently, after consideration of EPA's comments, PCA did not amend its test plan with regard to the proposed ecotoxicity testing. It should be noted that the ecotoxicity testing was conducted in accordance with the recommendations found in the Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD 2000).

In addition, given the extremely low solubility of both test materials, EPA's recommendation for a 21-day test using a flow-through method for even one of these substances would be impracticable. Based on the amount of water that would be required and the difficulty in performing the necessary serial analytical measurements, a flow-through test for rosin, methyl ester (or any other substances in this category) was simply not feasible. Thus, chronic aquatic toxicity testing in daphnia was not undertaken for this substance.

The ecotoxicity data are summarized in Table 11 below and demonstrate that rosin, PE ester is non-toxic to fish, daphnia and algae. Rosin, partially hydrogenated methyl ester was non-toxic to fish and algae, but demonstrated unexpected toxicity in daphnia. This finding was likely the result of insoluble fractions exerting a non-specific physical effect on daphnia since the solubility of all components of this substance was determined to be 2.10 mg/l. It should also be noted that samples for solubility determination and ecotoxicity testing were prepared in essentially the same way with the exception that for solubility samples were filtered prior to analysis. Finally, the unexpected result for rosin, partially hydrogenated methyl ester in daphnia is also contrary to EPA's prediction that *“other category members will not show aquatic acute or chronic effects based on their physiochemical properties.”*

Table 8

Chemical	Fish 96 hr *NOELr	Daphnia 48 hr NOELr	Algae 72 hr NOELr
Rosin, pentaerythritol ester	1000 mg/l	1000 mg/l	1000 mg/l
Rosin, partially hydrog. methyl ester	1000 mg/l	19 mg/l	1000 mg/l

*NOEL_r = No Observed Effect Loading Rate

These data are presented in greater detail in the Robust Summaries.

D. Human Health Effects Data

1. Acute Oral Toxicity

Acute oral toxicity studies investigate the effect(s) of a single exposure to a relatively high dose of a substance. This test is conducted by administering the test material to animals (typically rats or mice) in a single gavage dose. Harmonized EPA testing guidelines (August 1998) set the limit dose for acute oral toxicity studies at 2000 mg/kg body weight. If less than 50 percent mortality is observed at the limit dose, no further testing is needed. A test substance that shows no effects at the limit dose is considered essentially nontoxic. If compound-related mortality is observed, then further testing may be necessary.

Summary of Acute Oral Toxicity Data

One of the representative compounds, rosin, partially hydrogenated, methyl ester, as well as rosin, methyl ester are non-toxic following acute oral exposure with LD₅₀ values > 2,000 mg/kg in rats, guinea pigs and rabbits. An additional acute oral toxicity test (up-down procedure) on the other representative compound, rosin, pentaerythritol ester demonstrated an LD₅₀ value > 2,000 mg/kg in rats.

In their comments on the *Test Plan for Rosin Esters*, both EPA and Environmental Defense disagreed with the decision to conduct the acute toxicity test on rosin pentaerythritol ester since that substance had already been tested in both 90-day and lifetime cancer studies in rodents with a maximally tolerated dose of 5000 mg/kg/day. While this was a valid observation and would likely have resulted in

not conducting this test, due to the lateness of EPA's comments, this insight was not discovered and the acute toxicity test (up-down) had already been conducted.

2. Repeat Dose Toxicity

Subchronic repeat dose toxicity studies are designed to evaluate the effect of repeated exposure to a chemical over a significant period of the life span of an animal. Typically, the exposure regimen in a subchronic study involves daily exposure (at least 5 consecutive days per week) for a period of not less than 28 days or up to 90 days (i.e., 4 to 13 weeks). The HPV program calls for a repeat dose test of at least 28 days. The dose levels evaluated are lower than the relatively high doses used in acute toxicity (i.e., LD₅₀) studies. In general, repeat dose studies are designed to assess systemic toxicity, but the study protocol can be modified to incorporate evaluation of potential adverse reproductive and/or developmental effects.

Summary of Repeat Dose Toxicity Data

Existing data demonstrate low toxicity for rosin, pentaerythritol ester; rosin, glycerol ester; rosin, hydrogenated, glycerol ester; and rosin, hydrogenated, pentaerythritol ester in repeat dose tests. These studies, which are reviewed in detail in the robust summaries, demonstrate that the NOELs for these substances are 200 mg/kg/day or greater.

Rosin, pentaerythritol ester was tested in a 90-day subchronic toxicity study in rats. The test material was administered to male and female Sprague-Dawley rats at dietary concentrations of 0, 0.01, 0.05, 0.2, 1, or 5% for 90 days. The approximate doses were 0, 10, 50, 200, 1,000, or 5,000 mg/kg/day. Parameters evaluated included mortality, clinical signs, body weight, body weight gain, food utilization, food consumption, hematology, urinalysis, gross pathology, organ weights, and microscopic pathology.

Treatment did not affect body weight, body weight gain, clinical signs, hematology, urinalysis, gross or microscopic pathology. Food consumption was decreased at 5%, but food utilization was unaffected suggesting that the decrease in consumption was related to palatability. Absolute and relative liver weights were significantly increased in the high-dose males and females; however, no changes were observed at histopathology. Based on these data, the no observed effect level (NOEL) was 1% (approximately 1,000 mg/kg/day). Other 90-day subchronic studies confirm the low toxicity of rosin, pentaerythritol ester (see robust summaries).

Because none of the available data on one of the representative substances, rosin, pentaerythritol ester included a developmental toxicity component, an additional study (OECD 421) was undertaken to address this endpoint. Under the

conditions of this study the NOEL for both parental effects as well as reproductive and developmental effects was 20,000 ppm (approximately 1940 mg/kg/day).

The other representative substance in this category rosin, partially hydrogenated methyl ester was tested in a combined repeat dose reproductive/developmental toxicity study (OECD 422) at dietary dose levels of 5000, 10,000 and 20,000 ppm. Due to palatability issues, there was reduced body weight gain and food consumption at all dose levels throughout the study.² Mating performance and duration of gestation were similar in all groups, but at 20,000 ppm, there was a slight decrease in the mean number of implant sites per pregnancy.

At 5000 and 10,000 ppm, mean pup weights and mean litter weights were also lower than control. Minor changes in a few clinical chemistry parameters were noted, with a trend towards a dose related increase in calcium in males; increased alanine aminotransferase levels in males at 20,000 ppm; increased cholesterol in females at 20,000 ppm, and increased creatinine and bilirubin levels in females at 10,000 and 20,000 ppm. A dose related increase in liver weights in both sexes was associated with an increase in the incidence of hepatocellular hypertrophy across the groups. These findings were considered most likely to reflect an adaptive change in liver metabolism. There was no evidence of cell damage, cholestasis or changes to lipid metabolism revealed by histological examination, that would support the slight increases in alanine transferase, bilirubin and cholesterol levels, although these changes, and the increase in creatinine, may be related to the increased workload of the liver.

Due to reduced food consumption and body weights as a consequence of “severe” palatability issues at all dose levels, a parental or reproductive/developmental NOEL could not be derived from this study. However, it should be noted that all effects noted in this study were a direct consequence of reduced food consumption and body weight gain and the resulting metabolic stress placed on the liver.

In addition, other chemicals in this category (rosin, glycerol ester; rosin hydrogenated, glycerol ester; and rosin, hydrogenated, pentaerythritol ester) have also been confirmed to have low toxicity in 90-day subchronic studies. In these studies, the only effects noted were either death due to palatability resulting in non-consumption of food or depression of body weight gain at the highest doses tested. The NOELs in these studies ranged from approximately 1000 to 2,500 mg/kg/day.

² As noted in this study, *“Previous studies with Tall Oil and Rosin demonstrated that initially the animals prefer not to eat diet containing these items. This was considered to be indicative of a palatability issue; similar but less severe parental findings were noted in those studies.”*

3. Genotoxicity – In vitro

Genetic testing is conducted to determine the effects of substances on genetic material (i.e., DNA and chromosomes). The gene, which is composed of DNA, is the simplest functional genetic unit. Mutations of genes can occur spontaneously or as a consequence of exposure to chemicals or radiation. Genetic mutations are commonly measured in bacterial and mammalian cells, and the HPV program calls for completing both types of tests.

Summary of Genotoxicity Data

Rosin, pentaerythritol ester has been tested for potential carcinogenicity in a two-year bioassay conducted in rats. This study did not demonstrate any evidence of carcinogenicity. The primary effect was depressed weight gain at the highest dose, confirming that a maximally tolerated dose was achieved.

Since the purpose of *in vitro* bacterial and mammalian mutagenicity tests is to determine if a chemical might have the potential to be a direct-acting DNA reactive carcinogen, the negative carcinogenicity study eliminated the need to test rosin, pentaerythritol ester for potential genotoxicity.

In addition, rosin, glycerol ester has been tested for genotoxicity in several test systems including the Ames *Salmonella* assay, chromosomal aberrations in Chinese hamster ovary (CHO) cells and a rat primary hepatocyte assay to measure unscheduled DNA synthesis. None of these test systems showed any evidence of genotoxicity.

In reviewing the *Test Plan for Rosin Esters*, EPA disagreed with reliance on a negative 2-year carcinogenicity studies on rosin, PE ester (CAS# 8050-26-8) to fulfill the genotoxicity endpoint. This was based on the contention that this study failed to meet certain criteria for a cancer bioassay including group size, and the use of multiple exposure concentrations. While these observations might be correct, as described in the robust summary, the exposure was adequate to produce benign tumors in both the control and exposed groups. These results suggest that the dose level used was adequate to have produced a carcinogenic response if this substance was capable of causing malignant tumors.

In addition, EPA's comments also disagreed with the above statement that "*Since the purpose of in vitro bacterial and mammalian mutagenicity tests is to determine if a chemical might have the potential to be a direct-acting DNA reactive carcinogen, the negative carcinogenicity studies eliminate the need to test for potential genotoxicity.*" The comments then go on to list a number of genetic diseases and conditions (e.g., Down's syndrome, cystic fibrosis, hemophilia, sickle-cell anemia, allergies, mental retardation, etc.) with the implication that mutagenicity testing is able to predict the ability of a chemical to cause these adverse outcomes. There is no evidence that the two genotoxicity screening tests

that comprise the SIDS battery of tests (i.e., bacterial mutation and chromosomal aberration) have this ability. The likelihood that such testing would predict the non-cancer endpoints noted in EPA's comments is also tempered by the observation in Casarett & Doull's textbook on Toxicology (1996), *"No clear evidence exists for the induction of heritable alterations by radiation or chemicals in human germ cells."*

Finally, in the early stages of the HPV program, there was uncertainty about the format in which robust summary data would be submitted to EPA. In a meeting with Dr. Oscar Hernandez to discuss this issue, the summarized rosin data were used to illustrate a possible robust summary format. The above statement concerning the ability of negative carcinogenicity data eliminating the need to test for potential genotoxicity was included in the summarized data as part of this discussion. While Dr. Hernandez indicated that mutagenicity testing might indicate the potential for possible endpoints other than cancer, he readily agreed that for purposes of the HPV program, a negative cancer bioassay was a suitable surrogate for genotoxicity testing. Accordingly, bacterial gene mutation and chromosomal aberration testing on rosin, PE ester was not undertaken.

In reviewing the three robust summaries for the negative genotoxicity results for rosin, glycerol ester (CAS#8050-31-5), EPA concluded that the studies were inadequate since none tested concentrations up to the limits of toxicity or solubility. It should be noted that these results have been judged adequate to support a GRAS-like status for this substance.

Rosin, partially hydrogenated methyl ester was tested for genotoxicity in bacteria (OECD 471) and *in vitro* in mammalian cells (OECD 473). The genotoxicity data are summarized in Table 12 below and demonstrate that rosin, partially hydrogenated methyl ester is non-genotoxic in bacterial cells and non-clastogenic in mammalian cells both with and without metabolic activation.

Table 9

Chemical	Ames <i>Salmonella</i>		Chromosomal Aberration	
	+S9	-S9	+S9	-S9
Rosin, partially hydrogenated methyl ester	Neg.	Neg.	Neg.	Neg.

These data are presented in greater detail in the Robust Summaries.

4. Reproductive and Developmental Toxicity

Reproductive toxicity includes any adverse effect on fertility and reproduction, including effects on gonadal function, mating behavior, conception, and parturition. Developmental toxicity is any adverse effect induced during the period of fetal development, including structural abnormalities, altered growth and post-partum development of the offspring.

The “toxicity to reproduction” aspect of the HPV Challenge Program can be met by conducting a reproductive/developmental toxicity screening test or adding a reproductive/developmental toxicity screening test to the repeat dose study (OECD 421 or OECD 422, respectively).

Summary of Reproductive/Developmental Toxicity Data

As noted in the SIDS guidelines for the reproduction toxicity endpoint, *“when a 90-day repeated dose study is available and demonstrates no effects on the reproductive organs, in particular the testes, then a developmental study can be considered as an adequate test to complete information on reproduction/developmental effect.”* The following rosin esters have been tested in 90-day repeat dose studies: rosin, pentaerythritol ester; rosin, glycerol ester; rosin, hydrogenated, glycerol ester; and rosin, hydrogenated, pentaerythritol ester. In addition, rosin pentaerythritol ester has also been tested in a two-year bioassay. All of the 90-day studies and the two-year study included histopathology of reproductive organs (i.e., testes, ovaries, uterus).

One 90-day study on rosin, pentaerythritol ester reported testicular toxicity at 5,000 mg/kg/day; no adverse reproductive effects were observed at lower doses (i.e., 1,000 mg/kg/day and below). This result could not be replicated in a second 90-day study on rosin, pentaerythritol ester which revealed no testicular effects at doses up to and including 5,000 mg/kg/day. In addition, the two-year study showed no evidence of reproductive toxicity. The weight-of-evidence, i.e., (1) the lack of dose-response, (2) the lack of reproductive effects in a second study using the same compound, doses and design, and (3) the lack of reproductive effects in studies conducted on other rosin esters suggests that the testicular toxicity observed in the rosin, pentaerythritol ester study was an isolated finding and is not representative of the class of rosin esters.

Based on these data, it is concluded that the database of studies for the rosin esters satisfies the SIDS reproductive toxicity endpoint for one of the representative compounds. A developmental toxicity study using OECD Method 421 was conducted on rosin, pentaerythritol ester to complete the information on reproductive/developmental toxicity. As noted above, in this study the NOEL for reproductive and developmental effects was 20,000 ppm (1940 mg/kg/day). This study is reviewed in detail in the robust summaries.

Because there were no reproductive/developmental data for the other representative compound, rosin, partially hydrogenated, methyl ester, these endpoints were assessed in conjunction with repeat dose toxicity using OECD method 422. As reviewed above, due to severe palatability issues, a NOEL for reproductive/developmental toxicity could not be established. This study is reviewed in detail in the robust summaries.

IV. Category Justification: Validation of Rosin, Pentaerythritol Ester and Rosin, Partially Hydrogenated Methyl Ester as Representative of Other Category Members for SIDS Endpoints

All the members of this category of substances are esters of rosin, made by reacting rosin with selected alcohols or polyols at elevated temperatures to remove the water of reaction. However, because complete esterification is never achieved all rosin esters contain small amounts (ca 5%) of unreacted rosin.

Rosin, pentaerythritol ester and rosin, partially hydrogenated, methyl ester were selected as the representative substances in this category since these two substances represent the extremes of the properties of the members of this group. Pentaerythritol ester has the highest molecular weight and the methyl ester, the lowest. This molecular weight range manifests itself with the pentaerythritol ester having the highest softening point and the methyl ester the lowest. Consequently, the selection of these two substances as representatives of this category is consistent with the EPA guidelines since their molecular weights bracket the category.

The totality of data on the substances in this category demonstrates that the two representative substances are representative of all of the other substances. With respect to acute oral toxicity, the LD₅₀'s for rosin, pentaerythritol ester and rosin, partially hydrogenated methyl ester are both >2000 mg/kg. The LD₅₀ of >5000 mg/kg for rosin, methyl ester confirms that all are non toxic as measured by this endpoint. With respect to repeat dose and reproductive/developmental toxicity, the NOEL's for rosin, pentaerythritol ester and rosin, glycerol ester are 1000 mg/kg/day or greater. Due to severe palatability issues, a parental or reproductive/developmental NOEL for rosin, partially hydrogenated methyl ester could not be established although there were no adverse effects noted in this study that were not related to lack of food consumption and body weight effects. Finally, rosin, pentaerythritol ester was negative in a 2 year cancer feeding study, thus demonstrating a lack of genotoxic potential while rosin, glycerol ester and rosin, partially hydrogenated methyl ester were negative in *Salmonella* genotoxicity assays and chromosomal aberration assays in Chinese hamster ovary cells.

In summary, based on adequate toxicity data and a detailed understanding of the composition of the seven substances in this category, the data on rosin,

pentaerythritol ester and rosin, partially hydrogenated methyl ester (augmented by data on rosin, glycerol ester and rosin, methyl ester) can be reliably extrapolated to the entire category.

V. Hazard Characterization of Rosin Esters

For potential human health effects, the totality of the SIDS data demonstrate that rosin, pentaerythritol ester and rosin, partially hydrogenated methyl ester are non-toxic. Accordingly, based on the category approach, it can be inferred that all of the substances in this group are also non-toxic.

Neither rosin, pentaerythritol ester, nor rosin, partially hydrogenated methyl ester have acute oral toxicity (i.e., $LD_{50} > 2,000$ mg/kg), and repeat dose toxicity data on rosin, pentaerythritol ester (augmented by data on rosin, glycerol ester) demonstrate a no observed effect level (NOEL) of approximately 1000 mg/kg/day. The inability to establish a NOEL for rosin, partially hydrogenated methyl ester was due to severe palatability issues although it should be noted that all observed effects in this study were directly related to the lack of food consumption and resulting diminished weight gain. For rosin, pentaerythritol ester, there was no evidence of reproductive or developmental toxicity in the screening test (OECD 422) conducted in conjunction with the repeat dose toxicity study with a NOEL of approximately 2000 mg/kg/day. The NOEL of 1000 mg/kg/day for rosin, glycerol ester is confirmatory of the above findings. Rosin, pentaerythritol ester was negative in a 2 year cancer feeding study, thus demonstrating a lack of genotoxic potential while rosin, glycerol ester and rosin, partially hydrogenated methyl ester were negative in *Salmonella* genotoxicity assays and chromosomal aberration assays in Chinese hamster ovary cells. Consequently, no adverse health consequences would be associated with any anticipated exposures to any rosin esters in this category.

With respect to potential ecotoxicological effects, for rosin, pentaerythritol ester, the No Observed Effect Loading Rate (NOEL_r) for this substance on fish, daphnia and alga was 1000 mg/l. For rosin, partially hydrogenated methyl ester the NOEL_r for fish and algae was also 1000 mg/l; however, the NOEL_r for daphnia was 19 mg/l. This was likely due to non-specific toxicity from physical effects produced as a consequence of sample preparation, since the water solubility of this substance determined with an essentially identical method of sample preparation was only 2.10 mg/l.

VI. Potential Exposure to Rosin Esters

This brief summary provides an overview of market end uses and potential exposure to products derived from tall oil, a major feed stock to the pine chemicals industry with emphasis on rosins and rosin salts. This information along with hazard data developed as part of the High Production Volume Chemical Testing

Program is useful in evaluating the potential risks (if any) that might be associated with various uses of rosin esters.

Two primary fractions (rosin and fatty acids) are derived from the initial processing of tall oil. Tall oil rosin is consumed almost entirely in the production of other chemical intermediates. Rosin is reacted in a variety of ways to form salts, adducts, esters, dimers and other reaction products which find application in the production of printing inks, adhesives (primarily hot melt packaging adhesives), paper size, and coatings. These uses would be considered non-dispersive in that the rosin derived chemical is reacted or otherwise contained within the article in which it is being used. It is estimated that greater than 80% of the various rosin derivatives are used in the above type of applications where potential exposure is limited to contact with the article in which the rosin product is contained. As such inhalation exposure or volatilization to air is minimal. Exposure in the listed applications is generally limited to dermal contact during the processing, finishing and shipping of the products of which they become a part. Approximately 3% of rosin is reacted to form specific rosin esters (e.g., glycerol ester) which are marketed in to the chewing gum industry. These derivatives are approved for direct food contact by the US FDA

Human exposure is limited by the fact that virtually all rosin esters are industrial intermediates consumed in the production of other end products, mainly adhesives. As such there is little, if any, potential for exposure of the general consumer population. Environmental exposure is limited by the fact that the chemical processes used in the tall oil industry are essentially closed system processes where temperature and pressure are carefully controlled.

Environmental releases from tall oil processing plants are limited to (1) treated waste water discharge, and (2) ambient emissions following treatment with scrubbers or thermal oxidizers. Waste water can be generated from operation of the plant pressure control system or from minor spills and leaks associated with the process and/or handling of chemical products and routine housekeeping activities. In all cases the waste water is collected, the stream is treated to remove any free oil, and is then discharged into a larger biological waste treatment facility (either municipal treatment system or the treatment system of the paper mill). Any air emissions generated from the pressure control system or from the storage and transfer of various streams, are generally collected and treated in chemical scrubbers or thermal oxidizers.

The entire array of tall oil based chemicals and their related processing steps are best depicted by a "family tree" or flow diagram rather than a listing of discrete independent chemicals. Such a diagram demonstrates how various "parent" chemicals are consumed in the production of down stream chemicals. Consequently, it is inappropriate to sum production volumes. Figure 5 is a representation of the "family tree" for tall oil products and illustrates the

relationship between these products. Based on industry data approximately 95% of rosin is consumed during the production of other downstream products.

Table 10 illustrates general use categories and potential exposures to rosin esters. Of the various rosin esters, it is estimated that greater than 95% are consumed as intermediates in the production of the wide array of adhesives derived from these substances. Volatilization to air and hence inhalation exposure would be minimal due to the essential lack of a vapor pressure for these substances. Exposure in all of these industrial applications is generally limited to dermal contact during manufacture of the numerous products derived from rosin. The only other potential exposure to any of the substances in this category occurs during their production from activities such as changing reaction vessels, sampling for quality control, transferring material from one work area to another, loading and unloading bulk containers, changing filters, and cleaning equipment. The lack of water solubility of these compounds demonstrates that they are not bioavailable to aquatic organisms; this is confirmed by the lack of ecotoxicity to daphnia, fish and algae.

Figure 5
U.S. TALL OIL INDUSTRY

PRODUCTION & MARKET DISTRIBUTION
POUNDS/YEAR (000)

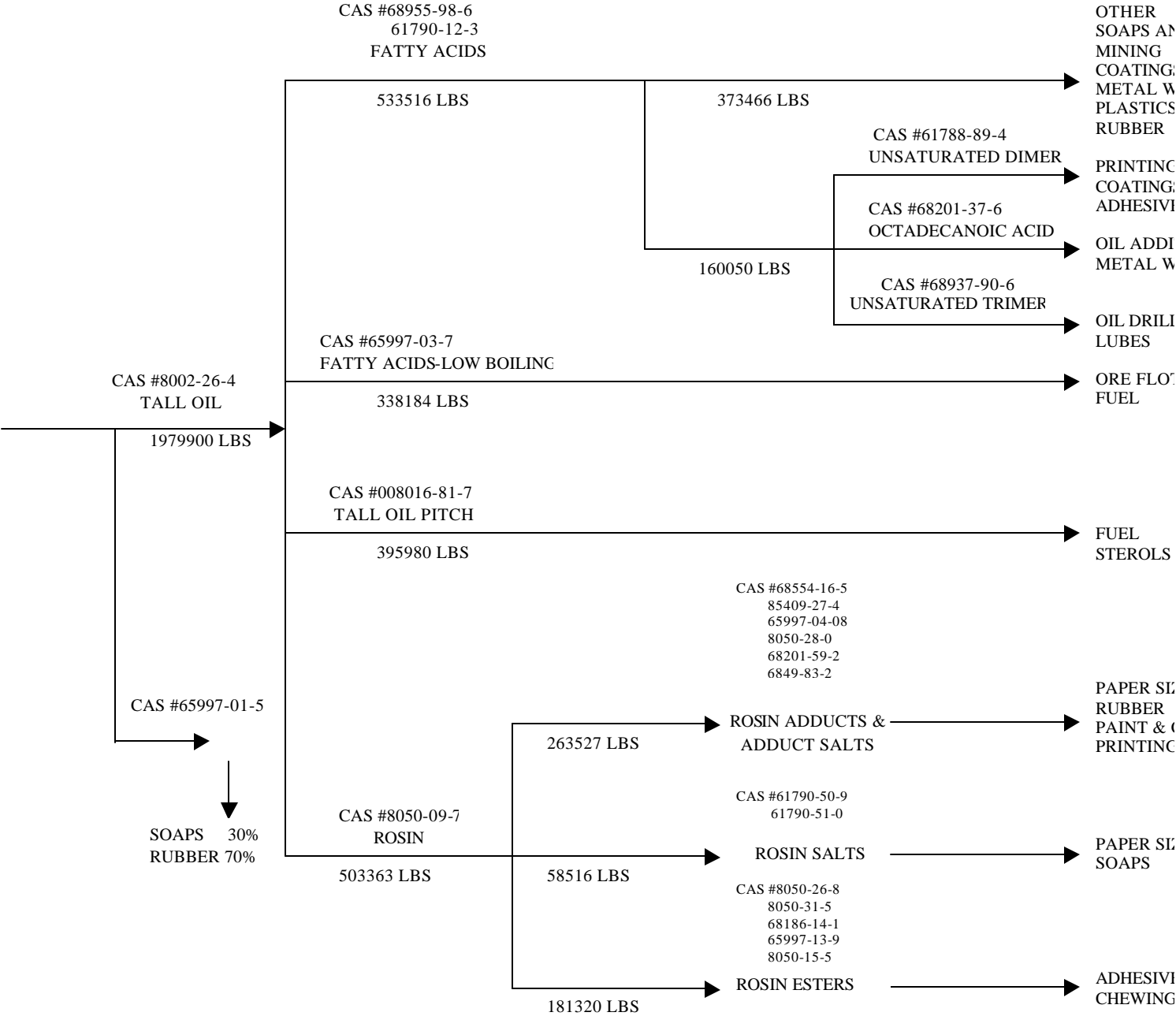


Table 10

Distribution, Application and Potential Occupational Exposure to Rosin Esters

Substance	CAS #	Primary Function	Use Category	Major End Use Application	%
Rosin, pentaerythritol ester	8050-26-8	Chemical intermediate (tackifier)	Site limited	Adhesives	100
Rosin, glycerol ester	8050-31-5	Chemical intermediate (tackifier)	Site limited	Adhesives	90
				Chewing gum	10
Rosin, diethylene glycol ester	68153-38-8	Chemical intermediate (tackifier)	Site limited	Adhesives	100
Rosin, methyl ester	68186-14-1	Chemical intermediate (tackifier)	Site limited	Adhesives	100
Rosin, hydrogenated glycerol ester	65997-13-9	Chemical intermediate (tackifier)	Site limited	Adhesives	100
Rosin, hydrogenated pentaerythritol ester	64365-17-9	Chemical intermediate (tackifier)	Site limited	Adhesives	100
Rosin, partially hydrogenated methyl ester	8050-15-5	Chemical intermediate (tackifier)	Site limited	Adhesives	100

References

Zinkel, D.F. and Russell, J., Eds. 1989. Naval Stores. Production, Chemistry, Utilization. Pulp Chemicals Association, New York.

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